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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,839	02/19/2002	Ajit Lalvani	7096-102XX / 10103632	3551

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EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/830,839	Applicant(s) LALVANI ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27-31,36-43,53-55,75,76,81 and 82* is/are allowed.

6)☒ Claim(s) *32-35,44-52,56-74 and 77-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 9sheets
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Examiner notes that upon further review and consideration of the claims, IPER, and Applicants' comments (filed May 16, 2003) in response to the Restriction Requirement (mailed April 22, 2003), the restriction requirement has been vacated. All claims, 27-82 will be examined in the pending application.

2. Claims 44-52, 58, 60-66, 72, 74 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44-52 and 60-66 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the kits do not set forth components or elements for detection. Presently the kit claims recite "kit for carrying out a method of determining infection in a human patient by.... comprising a peptide..."; the kit does not contain any components or elements for detection. The current claims directed to a kit only contain the peptide.

Claims 34, 49, 58, 65, 72 and 79 are vague and indefinite because it contains the use of an alternative expression wherein the limitation covers two different elements, i.e. "N-terminus" is not the same as "C-terminus". See MPEP 706.03(d), paragraph 5.

Claim 74 is vague and indefinite in the recitation of "capable"; it has been held that the recitation that an element is "capable of" performing a function is not

a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138.

3. Claims 32-35, 48-50, 56-59, 63-66 and 77-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining infection in an human patient by, or exposure of a human patient to mycobacterium which expresses ESAT-6 comprising the method of contacting a population of T cells from the patient with the peptide represented by SEQ ID NO: 1 (ES1) and optionally other peptides from SEQ ID NO: 2-11, and a kit for carrying out the method, does not reasonably provide enablement for methods of determining infection in an human patient by, or exposure of a human patient to mycobacterium which expresses ESAT-6 comprising the method of contacting a population of T cells from the patient with the peptide represented by SEQ ID NO: 1 (ES1) and optionally other peptides from SEQ ID NO: 2-11, wherein the peptide is substituted by an analogue, the peptide analogue has one or more deletions or conservative substitutions and a kit for carrying out the method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses subjects studied in Example 1 (p. 16), results using ELISPOT assay in Example 2 (p. 17) and demographic and clinical features of patients and controls in Example 3 (p. 19). The specification also discloses detection of CD4 T cell responses in healthy contacts in Example 4 (p. 24), detection of CD4 T cell responses in healthy contacts using a different panel (SEQ

ID NO: 1-6, 8, 9) in Example 5 (p. 24) and sensitivity of the panel in comparison with use of whole ESAT-6 in Example 6 (p. 25).

The specification does not enable any method of detection wherein an analogue to the claimed peptides has been used. The specification does not teach the use of peptide analogues wherein one or more substitutions and/or deletions have been made to the peptides in the claimed method of detection. It is noted that the analogue description appears to be a mere paper protocol (see specification pages 9-11) and no analogue peptides have been made or used in the methods described/used in Examples 1-5.

It is noted that a peptide can be considered a functional equivalent of another peptide for a specific function if the equivalent peptide is immunologically cross-reactive with and has at least substantially the same function as the original peptide. The specification also sets forth examples of possible amino acid substitutions and that analogues can have a greater or lesser degree of homology as between the analogue amino acid sequence and the original.

However, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In

view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of analogues encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

It is **not** routine in the art to screen for positions within the protein's sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure (see Bowie et al., Science, Vol 247, pp 1306-1310, especially p. 1306, column 2, paragraph 2 and Kumar et al. PNAS 87: 1337-1341 February 1991. One skilled in the art would expect any tolerance to modification shown for a given protein/peptide to diminish with each further and additional modification, e.g. multiple deletions or substitutions. The sequence of some proteins/peptides is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins/peptides. The specification does not support the broad scope of the claims, which encompass a multitude of polypeptides because the specification does **not** disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified;
  -which regions are protective; and
- essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed polypeptides in manner reasonably correlated

with the scope of the claims broadly including any number of deletions, additions, substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The specification does not support the broad scope of the claims which encompass all variants/analogues of the peptide and possibility of changing one or more amino acids to any one of 23 different amino acids because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants/analogues, if any, can be made which retain the biological activity, claimed activity and immunogenicity of the intact peptides; and the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The claimed methods and kits as set forth in claims 32-35, 48-50, 56-59, 63-66 and 77-90 are not enabled for the reasons as set forth above.

4. Claims 67-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to pharmaceutical compositions

comprising a peptide panel consisting of SEQ ID NO: 1 and one or more peptides from SEQ ID NO: 2-11 together in a pharmaceutically acceptable carrier. Other claims are also directed to pharmaceutical compositions comprising peptides that have been substituted by an analogue (substitution, deletion or addition of one or more amino acids of the peptide(s)). The claims also recite "...said peptides is substituted by a peptide analogue which has one or more deletions at the N-terminus and/or C-terminus...".

As previously stated, the specification discloses subjects studied in Example 1 (p. 16), results using ELISPOT assay in Example 2 (p. 17) and demographic and clinical features of patients and controls in Example 3 (p. 19). The specification also discloses detection of CD4 T cell responses in healthy contacts in Example 4 (p. 24), detection of CD4 T cell responses in healthy contacts using a different panel (SEQ ID NO: 1-6, 8, 9) in Example 5 (p. 24) and sensitivity of the panel in comparison with use of whole ESAT-6 in Example 6 (p. 25). It is noted that all examples set forth in the specification are directed to the method of determining infection in a human patient using the SEQ ID NO: 1 and SEQ ID NO: 2-11.

The claims recite a pharmaceutical composition, however, it is not clear what its particular use is. The Examiner interprets that the composition will be used as a vaccine to protect against tuberculosis in view of the need for a more protective vaccine as asserted in the prior art. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. See MPEP 2164.01(c). The specification is not enabled for the pharmaceutical compositions as presently claimed. The art is replete with studies that show that whole ESAT-6 is able to provide protection at the level of BCG protection (see Andersen, 2000 and Young, 2003 for example). Skjot et al, 2001

describe that research on the fine specificity of human T-cell responses to the ESAT-6 family members using panels of overlapping peptides has demonstrated that even though the antigens are small molecules they contain several T-cell epitopes and that these epitopes will be of major importance in relation to vaccine design, as an effective subunit vaccine should contain multiple epitopes to ensure broad coverage of a genetically heterogenous population (p. 644). Applicants have indicated that amino acids 1-15 of ESAT-6 (ES1) are the most important; it is used in all methods and pharmaceutical compositions. However, the peptide (ES1) is set forth by Applicant as being able to provide protection are not taught in the prior art. Olsen et al 2000 teaches that vaccines based on subdominant ESAT-6_{51-70} epitope promoted significant levels of protective immunity and that the level of protection was equivalent to that achieved with ESAT-6 and BCG (abstract; p. 1727, col. 2). The ESAT-6_{1-20} of Olsen et al is similar to Applicant's ES1, but the Oslen et al peptide did not provide protection. The peptide comprising amino acids 1-15 do not show protection as predicted by Applicants' specification. The prior art teaches that key epitopes on the ESAT-6 protein provide protective immunity, however, not all possible peptide panels as suggested by the claims would provide such protection (see Brandt et al 1996, J. Immunology, 157:3527-3533; Olsen et al, 2000, Eur. J. Immunology, 30:1724-1732).

The claimed invention appears to indicate a pharmaceutical use (i.e. vaccine) for the claimed composition. However, the specification has not enabled such a composition. The specification has described at page 15 a pharmaceutical composition but no actual enablement for using the peptides has been set forth. The specification must teach how to make the claimed composition without undue experimentation and must teach how to use the composition for at least one

pharmaceutical use without undue experimentation. It is noted that a pharmaceutical composition should have some pharmaceutical use; use as a drug or therapeutic agent. A therapeutic agent is considered any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal. A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body.

Further, with regard to the peptide analogues, Houghten et al teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the variants or derivatives that retain immunodominant regions and immunological activity if the regions have been altered. It is known in the art that amino acid changes/variations of a peptide will affect its properties; "... alterations in the chemical nature of an amino acid within a site (e.g., reversal, removal or creation of a charge, elimination of a hydrogen bond, etc.) brought about by chemical modifications or evolutionary replacement in a homologous protein of a different

species would reduce or abolish the reactivity of the site." (Bixler et al, p. 56, para. 1). The determination of substitutions, deletions, and other undescribed and/or undefined "modifications" that result in derivatives which retain the immunological activity of the immunodominant region would require undue experimentation for a person of ordinary skill in the art. See M.P.E.P. §§ 706.03(n) and 706.03(z).

For the reasons set forth above, the pharmaceutical composition as claimed is not enabled.

5. Claims 27-31, 36-43, 53-55, 75, 76, 81 and 82 appear to be in condition for allowance.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, see Form 892.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
July 22, 2003